39. *Optically Active Alkylsuccinic Acids. Part II. The Stereochemical Configuration of the Symmetrical Diethylsuccinic Acids.*

By Henry Wren and John W. E. Haller.

Although the symmetrical dialkylsuccinic acids have been frequently investigated, the stereochemical configuration has been elucidated only in the case of the dimethyl acids, of which the isomeride of lower melting point has been resolved into its optical antipodes by Werner and Basyrin (*Ber.*, 1913, **46**, 3229). In the case of the *s*-diethylsuccinic acids the preparation of the isomeride, m. p. 190—192°, by the reduction of xeronic (diethylmaleic) acid (Otto, *Annalen*, 1887, **239**, 279) indicates that it probably has the *meso*-configuration, but the significance of this observation appears to have been overlooked by subsequent workers, most of whom have believed that the isomeride of lower melting point is the *meso*-

form as with the tartaric acids. Recent determinations of the heats of combustion of the dimethyl-, diethyl-, and diphenyl-succinic acids and their derivatives (Verkade and Hartman, *Rec. trav. chim.*, 1933, **52**, 9) show that if the diethylsuccinic acid, m. p. 130°, is regarded as the *r*-compound its properties resemble those of the proved *r*-dimethyl- and *r*-diphenyl-succinic acids (Wren and Still, J., 1915, **107**, 444) with respect to the mutual transformations of the *r*- and *meso*-acids and anhydrides, that in all cases the *r*-acid has the lower melting point, greater solubility in water at 25° and smaller energy content, but the values of the dissociation constants of the diethylsuccinic acids are oppositely situated to those of the corresponding dimethyl- and diphenyl-succinic acids.

The resolution of the *s*-diethylsuccinic acids has been examined in considerable detail by Bischoff (*Ber.*, 1891, **24**, 1068), who was unable to obtain evidence of activity by fractional crystallisation of the morphine salt of the acid, m. p. 190—192°, or by the action of *penicillium glaucum* on the acid. He found that the brucine, cinchonine, quinidine, morphine and strychnine salts of the acid, m. p. 130—132°, are not sufficiently crystalline for use in attempted resolutions, and that the acid is not attacked by *Penicillium glaucum.* He concluded that rotatory power depends on " the specific difference of the residues attached to the asymmetric carbon atom and that this difference is more marked when these groups are H, OH and CO_2H than when they are H, C_2H_5, CO_2H." On this account, therefore, he suggested that diethylsuccinic acid might be expected to have a lower rotatory power than tartaric acid, and that the difference in the solubilities of the alkaloidal salts of the two optically active isomerides would be less than in the case of the tartaric acids, so that separation of these salts by fractional crystallisation would be much more difficult, and perhaps impossible by known methods. The present experiences differ from those of Bischoff in that it has been found that the acid, m. p. 130—132°, under suitable conditions yields well-crystallised salts with brucine, cinchonine, morphine, cinchonidine, strychnine and, to a less extent, with quinine, and that resolution into its optical antipodes can be effected with brucine or cinchonine, although the process is more tedious than usual. It is thus established that the acid, m. p. 130—132°, is the racemic, and that of m. p. 190—192°, the *meso*-variety. In the cases of the dimethyl-, diethyl-, diphenyl-, and dibromo-succinic acids (McKenzie, J., 1911, **99**, 150; 1912, **101**, 1196; Holmberg, *Svensk Kem. Tidskr.*, 1911, No. 5; *J. pr. Chem.*, 1911, **84**, 145) the isomeride of lower m. p. is the racemic form, whereas the reverse is true with tartaric and dimethoxysuccinic acid.

The *s*-diethylsuccinic acids were first isolated by Hell (*Ber.*, 1873, **6**, 30) from the products of the action of methyl iodide and molecular silver on ethyl α-bromobutyrate, and subsequently obtained by Hell and Mühlhäuser (*Ber.*, 1880, **13**, 473) from silver and ethyl α-bromobutyrate only. Later, they were obtained by Bischoff and by Hjelt (*Ber.*, 1887, **20**, 2989, 3078; 1888, **21**, 2085, 2089) either from ethyl α-bromobutyrate and ethyl sodioethylmalonate or from the latter and ethyl chloromalonate; the recorded yields are only about 30% of the theoretical and the reactions are complicated by the production of glutaric derivatives (cf. von Auwers and Jackson, *Ber.*, 1890, **23**, 1599; Bone and Sprankling, J., 1899, **75**, 842). More satisfactory results in the preparation of certain alkyl-substituted succinic acids have been obtained by Bone and Sprankling (*loc. cit.*; J., 1900, **77**, 654, 1298) and by Bone, Sudborough, and Sprankling (J., 1904, **85**, 534) by replacing ethyl malonate and its homologues by ethyl cyanoacetate and its derivatives. This method has been extended by us to the *s*-diethylsuccinic acids by condensing ethyl cyanoacetate with sodium ethoxide and ethyl α-bromobutyrate to give ethyl α-cyano-β-ethylsuccinate, the sodium derivative of which is transformed by ethyl iodide into ethyl α-cyano-αβ-diethylsuccinate which is hydrolysed to the required acids. After the completion of this part of the work a similar method was described by Verkade and Hartman (*loc. cit.*), who, however, gave neither experimental details nor particulars of yield.

Preliminary trials were made, using ethyl acetoacetate. The condensation of ethyl sodioethylacetoacetate with ethyl α-bromobutyrate did not proceed very satisfactorily in ethyl alcohol, but the crude ethyl α-acetyl-αβ-diethylsuccinate gave when hydrolysed small amounts of the isomeric diethylsuccinic acids. Ethyl acetoacetate condensed readily with ethyl α-bromobutyrate, giving ethyl α-acetyl-β-ethylsuccinate, b. p. 157°/10 mm., in about 64% yield. This could not be ethylated by sodium and ethyl iodide in dry ether (cf.

Thompson, J., 1932, 2314), whereas in ethyl alcohol it afforded ethyl α-acetyl-αβ-diethylsuccinate, b. p. 167—169°/8 mm., in about 23% yield. This was treated catalytically with sodium ethoxide in ethyl alcohol (cf. von Miller, *Annalen*, 1880, **200**, 281; Dieckmann, *Ber.*, 1900, **33**, 261; Dieckmann and Kron, *Ber.*, 1908, **41**, 1266), giving ethyl acetate and ethyl diethylsuccinate, which was then hydrolysed by dilute alcoholic potash, but the results so obtained were less satisfactory than those given by direct hydrolysis with concentrated alcoholic potash. The over-all yields of the required acids were much lower than those obtained by the cyanoacetate method, so the work in this direction was not pursued further.

EXPERIMENTAL.

A solution of ethyl cyanoacetate (113 g.) in anhydrous alcohol (100 c.c.) was added slowly and with constant, vigorous shaking to a well-cooled solution of sodium (23 g.) in alcohol (320 c.c.), and ethyl α-bromobutyrate (200 g.) was slowly run in to the cold mixture. During the addition the temperature should not be allowed to rise. Subsequently the mixture was left with frequent shaking for about ½ hour, and then heated on the water-bath until a test portion was neutral to phenolphthalein. The alcohol was removed in a brine bath, the residue mixed with water, extracted with ether, the extract dried (calcium chloride), and the ether removed; on distillation, ethyl α-cyano-β-ethylsuccinate, b. p. 164°/21 mm., was obtained in 67% yield. A solution of this ester (100 g.) in alcohol (70 c.c.) was added slowly to sodium (10·13 g.) in alcohol (170 c.c.) and the product was treated gradually with ethyl iodide (69 g.); the mixture was heated on the water-bath until a test portion was neutral to phenolphthalein, after which excess of ethyl iodide and alcohol were removed by heating in a brine bath. The residue was diluted with ether, and the solution was thoroughly washed with water to remove a coloured impurity which otherwise passes into the finished product. The ethereal solution was further washed with concentrated brine, dried over calcium chloride and distilled, whereby ethyl α-cyano-αβ-diethylsuccinate, b. p. 167—170°/18 mm., was obtained in 79% yield, together with smaller amounts of more volatile material.

Hydrolysis and removal of the cyano-group from esters of this type proceeds with some difficulty. Bone and Sprankling (*loc. cit.*) in analogous cases recommend a two-stage process whereby the ester is first hydrolysed with alcoholic potash, and the cyano-acid is then treated with 50% sulphuric acid, whereas Verkade and Hartman (*loc. cit.*) use prolonged boiling with 20% hydrochloric acid, but do not give any particulars of yield. An almost quantitative hydrolysis can be obtained comparatively rapidly by the following procedure, which requires somewhat careful supervision, since too drastic treatment causes considerable carbonisation, whereas less rigorous conditions do not lead to complete hydrolysis. Concentrated sulphuric acid (24·4 c.c.) was added slowly and with vigorous shaking to the ester (30·1 g.) contained in a flask fitted with a ground-in air-condenser. Much heat was developed, and the flask was cooled somewhat after two-thirds of the acid had been added. The resultant yellow liquid was left for five minutes, after which water (6 c.c.) was slowly added and the flask was cautiously heated on a sand-bath. Brisk evolution of carbon dioxide occurred, and the temperature was slowly increased as the evolution of gas slackened. After ten minutes' heating, the flask was allowed to cool somewhat, and a further 6 c.c. of water were added dropwise and very cautiously through the air-condenser. When the vigorous ebullition caused by this addition had subsided, heating was continued for a further 15 minutes, after which 6 c.c. of water were added and boiling continued for a further 1½ hours. After addition of 25 c.c. of a mixture of concentrated sulphuric acid (25 c.c.) and water (20 c.c.), boiling was continued for two hours, after which the mixture was allowed to cool with frequent shaking. The crystals were removed on a sintered-glass filter, and washed repeatedly with small quantities of cold water. The combined filtrate and washings (about 200 c.c.) were boiled under a reflux condenser for 3 hours, thus giving a second crop which was removed and washed. The filtrate and washings were finally extracted with ether. The first two crops together weighed 18·1 g., and a further 2·4 g. were obtained from the ether. This last portion contained a very small amount of oily matter, which was readily removed by washing with a little cold benzene. The mixture of acids thus obtained was dissolved in boiling water; after decolorisation (animal charcoal), the solution deposited a crop of mixed acids, whilst further portions were obtained by concentration of the filtrate, and finally by extraction of it with ether. Treatment of the crops with boiling benzene left a residue of *meso*-diethylsuccinic acid, m. p. 190—192°, which is readily purified, if necessary, by crystallisation from water. The benzene solutions on cooling deposited *r*-diethylsuccinic acid, m. p. 130°. The final yields of homogeneous acids were 2·95 g. and 13·05 g. respectively.

Resolution of r-*Diethylsuccinic Acid into its Optical Antipodes.*—*r*-Diethylsuccinic acid (25 g.) and anhydrous brucine (113 g.) were dissolved in a hot mixture of rectified spirit (150 c.c.) and water (600 c.c.). On cooling, the solution readily deposited a well-crystallised crop (113·0 g.), which was purified by repeated crystallisation from 20% alcohol. The course of the resolution was followed by observation of the specific rotation of the acid recovered from the successive mother-liquors, the following values of $[\alpha]_{5461}$ in acetone being observed: − 22·6°, − 21·7°, − 14·8°, − 8·5°, − 2·3°, + 2·7°, + 10·4°, + 15·1°, + 23·8°, + 23·9°, + 27·8°, + 30·8°, and + 30·2°. The final crop of brucine salt (12·3 g.) gave 2·0 g. of the crude *d*-acid, with $[\alpha]_{5461}^{24^\circ}$ + 32·8° in acetone ($c = 5$).

Crystallisation of it from boiling benzene yielded d-*diethylsuccinic acid*, m. p. 125°, $[\alpha]_{5461}^{24^\circ}$ + 34·5°, or $[\alpha]_{\text{Hg yellow}}^{24^\circ}$ + 30·9° in acetone; its specific rotation remained unchanged after further crystallisation [Found: 0·1004 g. of acid neutralised 22·87 c.c. of 0·05056*N*-$Ba(OH)_2$. $C_8H_{14}O_4$ requires 22·81 c.c.].

For the isolation of the pure *l*-acid the crude lævorotatory mixtures obtained in the above resolution were converted into the brucine salts, which were recrystallised from boiling 20% alcohol. The *l*-acid was thereby concentrated in the filtrate, from which it was removed and recombined with brucine, the process being continued until a sample with $[\alpha]_{5461}$ − 31·4° in acetone was obtained. Even when the mixture contains relatively little of the *d*-acid, crystallisation of the salts proceeds satisfactorily, although slowly. Recrystallisation of the sample from boiling benzene gave l-*diethylsuccinic acid*, m. p. 125°, $[\alpha]_{5461}^{25^\circ}$ − 34·3°, $[\alpha]_{\text{Hg yellow}}^{25^\circ}$ − 30·7° in acetone [Found: 0·1005 g. neutralised 23·00 c.c. of 0·05056*N*-$Ba(OH)_2$. $C_8H_{14}O_4$ requires 23·05 c.c.].

The solubility of the active acids is much greater than that of the *r*-acid, and it appears essential that the active material should have about $[\alpha]_{5461}$ ± 30° in acetone before the final purification from boiling benzene can be successfully accomplished. For instance, a sample, $[\alpha]_{5461}$ + 28·0° in acetone, when crystallised from benzene gave a product with $[\alpha]_{5461}$ + 26·8°, whereas that recovered from the mother-liquor had $[\alpha]_{5461}$ + 29·8°.

The resolution of *r*-diethylsuccinic acid by means of cinchonine in hot aqueous solution gave less satisfactory results. With molecular and half-molecular quantities of the alkaloid, the normal salt of the *d*-acid separated; crystallisation occurred less readily, and the resolution appeared to proceed more slowly than when brucine was employed.

MUNICIPAL COLLEGE OF TECHNOLOGY, BELFAST.

[*Received, December* 1*st*, 1936.]